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Health and Environmental Effects Profile for Trifluralin

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR TRIFLURALIN

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16. ABSTRACT

The Health and Environmental Effects Profile for trifluralin was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Trifluralin has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for trifluralin is 2.9×10^{-2} (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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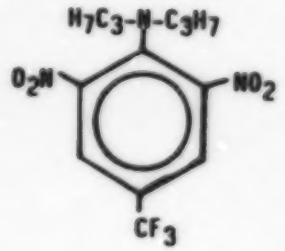
LIST OF ABBREVIATIONS

α	Alpha
BCF	Bioconcentration factor
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppb	Parts per billion
ppm	Parts per million
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Trifluralin is also known as Treflan; Triflurex; Treficon; Trifluoralin; Trefanocide; Trifluraline; Elancolan, alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine; N,N-di-n-propyl-2,6-dinitro-4-trifluoromethylaniline; 4-(di-n-propylamine)-3,5-dinitro-1-trifluoromethylbenzene; and 2,6-dinitro-N,N-dipropyl-4-(trifluoromethyl)-benzenamine (U.S. EPA, 1979). The structure of trifluralin is given below:



Molecular formula: $C_{13}H_{16}F_3N_3O_4$

Molecular weight: 335.3

The Chemical Abstracts Service (CAS) Number for trifluralin is 1582-09-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Trifluralin is a yellow-orange solid at ambient conditions. Some of its chemical and physical properties are given below (Verschueren, 1983):

Melting point:	48.5-49°C
Boiling point:	139-140°C at 4.2 mm Hg
Vapor pressure:	1.99×10^{-4} mm Hg at 29.5°C
Water solubility at 27°C:	4 ppm
BCF:	1060-6000 in fish

The log K_{ow} has been reported to be 5.3 (Briggs, 1981).

1.3. PRODUCTION DATA

Trifluralin is produced by the nitration of 1-chloro-4-trifluoromethylbenzene and reaction with dipropylamine (Martin and Worthing, 1977). Eli Lilly of Lafayette, IN, was listed as the sole United States producer of trifluralin in 1982 (SRI, 1983). It was estimated that at least 24 million pounds of trifluralin were produced in 1975 (Ayers et al., 1976).

1.4. USE DATA

Trifluralin is a dinitroaniline herbicide used to control annual grasses and some broadleaf annual weeds (e.g., foxtails, panicums, crabgrass and barnyard grass) on a variety of crops, shrubs and flowers. Trifluralin is used on cotton (70% of total United States cotton acreage), soybeans (38% of total United States soybean acreage) and fruits and vegetables (2% of total United States acreage) (U.S. EPA, 1979).

The major formulation of trifluralin in use is an emulsifiable concentrate. Small amounts of a granular formulation are also used (U.S. EPA, 1979). Trifluralin is applied by hand or machine broadcast, low pressure surface sprays and subsurface layering at rates between 0.25-4.0 pounds/acre (U.S. EPA, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Trifluralin can enter the atmosphere as an aerosol from spray application, or when volatilized from soil. The evaporation rate of freshly applied trifluralin from soil is rapid (>30 g/ha/day) (Nash, 1983) and is associated with increasing temperature (Spencer and Cliath, 1974), soil moisture content (U.S. EPA, 1979) and soil concentration (Hollingsworth, 1980).

White et al. (1977) evaluated trifluralin volatilization losses from a soybean field in Georgia. Air samples collected above treated (1.1 kg trifluralin/ha) and tilled soil contained 16,500 ng trifluralin/m^3 before incorporation, 3400 ng/m^3 after incorporation and <100 ng/m^3 after day 35. The loss of trifluralin via vaporization over a 120-day period was estimated to be ~26% of the amount applied.

Soderquist et al. (1975) evaluated the volatilization and photodecomposition of trifluralin under laboratory and field conditions. An air sample collected over a field of soil incorporated (to 15 cm depth) with trifluralin (0.9 kg/ha) contained 11.7 ng trifluralin/m^3 1 day after application. Air samples collected over a plot to which trifluralin was surface-applied 2.8 days earlier contained ~30-60 ng trifluralin/m^3. These results are in accordance with the manufacturer's recommendations; 3-4 times as much trifluralin is needed when surface applied, compared to soil incorporation (Soderquist et al., 1975). In the soil incorporation experiment, an air sample collected after rainfall (5 days after application) contained >150 ng trifluralin/m^3. An air sample collected over the surface-applied trifluralin plot contained >2550 ng trifluralin/m^3 after application of water to the surface. Four vapor phase photodecomposition products were collected from the air over the soil plot that was surface-

treated with trifluralin. These showed oxidative dealkylation and cyclization to indole type products. Laboratory experiments conducted with trifluralin-coated dust in a vapor phase reactor indicated that the occurrence of vapor phase photolysis products, although soil surface photolysis followed by volatilization was postulated to occur to a greater extent. When trifluralin was coated onto standard test dust, suspended in air and irradiated with an RS sunlamp (spectral contribution <300 nm filtered out), a half-life of 2.5 hours was observed (Soderquist et al., 1975).

Woodrow et al. (1978) studied the photooxidation of trifluralin released as a spray in a field trial. Air samples collected downwind of the release point contained a dealkylated photoreaction product, 2,6-dinitro-N-propyl-alpha, alpha,alpha-trifluoro-p-toluidine. The estimated half-life (t 1/2) of the reaction ranged from 21 minutes in August to 193 minutes in October. A laboratory experiment indicated that trifluralin was stable in the dark but it was rapidly photodegraded by light from a Xenon arc lamp (t 1/2 = 117 minutes), especially in the presence of 1-3 ppm ozone (t 1/2 = 47 minutes).

The fate and transport of trifluralin in soil has been studied extensively. The persistence and degradation of trifluralin in soil is dependent upon many factors, including temperature, moisture, incorporation method and the amount of organic matter present (U.S. EPA, 1979).

Trifluralin has been reported to photodegrade rapidly when present at the soil surface in laboratory and field trials (Soderquist et al., 1975), although Plimmer (1978) reported little photolysis of trifluralin when soil-coated plates were treated and irradiated in summer sunlight. Parochetti and Hein (1973) observed little photodecomposition when trifluralin treated sand was irradiated for 72 hours with a 290-340 nm UV lamp. Parochetti and

Dec (1978), however, observed the photodecomposition of trifluralin on soil thin layer plates to be ~18% in 7 days.

Microbial degradation of trifluralin in soil undoubtedly occurs, since significantly greater decomposition was observed in unsterilized soil when compared with sterilized soil (Sanborn et al., 1977). Metabolic products were observed when trifluralin was incubated with sewage, but not with sterile sewage (Jacobson et al., 1980). Trifluralin also has been reported to undergo degradation in soil under anaerobic and aerobic conditions (Parr and Smith, 1973; Wheeler et al., 1979).

Camper et al. (1980) reported that trifluralin underwent degradation when incubated in two soil types under aerobic and anaerobic conditions. Radiolabeled (^{14}C) trifluralin was applied (1 ppm) to loamy sand and clay loam soils. Sterilized and viable samples of these soils were incubated for up to 4 months under aerobic and flooded (anaerobic) conditions. No degradation was observed in sterile controls; all recovered radioactivity was in the form of the parent compound. Rates of degradation in the nonsterile soils were dependent upon incubation time and soil type. The greatest extent of trifluralin degradation occurred in fungi-rich Cecil loamy sand under aerobic incubation, with 83% degradation after 4 months. Aerobic and anaerobic incubation in Goldsboro loamy sand accounted for >80% degradation, based on products formed after 3 months. In Drunmer clay loam soil, anaerobic and aerobic incubation accounted for ~45 and ~75% degradation based on products formed, respectively.

Hamdi and Tewfik (1969) reported the removal of nitro-groups from trifluralin during microbial degradation by a pseudomonad. Carter (1973) detected four N-dealkylated degradation products of trifluralin when it was incubated in the presence or absence of Pseudomonas florescens. The soil

microflorae, Fusarium solani and Pseudomonas sp., were found to grow well when incubated with trifluralin as the sole source of carbon and nitrogen (Carter, 1973).

Spain (1983) reported that microorganisms in water and sediment samples did not adapt to trifluralin. The author postulated that if released in a river, trifluralin would biodegrade at a slow, concentration-dependent rate.

Willis et al. (1974) reported enhanced degradation of trifluralin in soil suspensions having reduced oxidation reduction potential. Probst and Tepe (1969) reviewed the degradation of trifluralin, and concluded that trifluralin is degraded by soil microbes, but concluded that there is no evidence that this is the primary route of degradation.

Carryover of soil-applied trifluralin to the next growing season has been observed in field studies by Golab et al. (1979), Smith and Hayden (1976, 1982), Hayden and Smith (1980), Miller et al. (1975), Solbakken et al. (1982), Probst et al. (1967) and Jensen and Kimball (1980). LaFleur et al. (1978) applied 2 kg trifluralin/ha to plots of Congaree sandy loam soil and measured the residues in the 0-20 cm layer for up to 1024 days. A two-phase first order decay was observed, with half-lives for the first and second phase of 19 and 450 days, respectively. The soil concentrations of trifluralin on day 0 and day 1024 were 1.24 and 0.08 μmol/kg, respectively.

Substantial sorption of trifluralin to soil particulates can be predicted from the compound's relatively high log octanol/water partition coefficient (log K_{ow} = 5.3) (Briggs, 1981). Trifluralin is bound to soil possessing high organic matter content (Kearney et al., 1977; Jacques and Harvey, 1979). Golab et al. (1979) found <1.5% of the trifluralin applied to field soil after 3 years. Various transformation products accounted for 4%, and soil-bound residues accounted for 38% of the applied compound.

Wheeler et al. (1979) reported that an increased percentage of trifluralin and/or its metabolites became bound to sandy loam soil over time. McCall et al. (1981) reported high soil sorption coefficients (3000-5360) and observed little leaching of trifluralin in soil column experiments. Leaching of trifluralin and its metabolites in soil cores taken from field plots treated with the compound was not observed (Golab et al., 1979). Mosier and Sanders (1977) classified trifluralin as highly resistant to leaching. Kenaga (1980) reported experimental and calculated soil adsorption coefficients for trifluralin of 13,700 and 5800, respectively. This indicates tight binding of the compound to soil organic matter and predicts little potential leachability.

Rohde et al. (1980) studied the surface and subsurface losses of trifluralin applied to a Georgian loamy-sand watershed. The compound was applied (1.1 kg/ha) and incorporated to a depth of 10 cm. Negligible amounts of trifluralin were found in the shallow subsurface flow, and surface runoff accounted for 0.17 and 0.03% of the amount applied in 1974 and 1975, respectively. Willis et al. (1975) reported a maximum seasonal runoff loss of 0.05% of the trifluralin applied to agricultural land in the lower Mississippi River Valley. Sheets et al. (1972) found that <1% of the applied trifluralin was detected in runoff water from cotton plots. Trifluralin adsorbed to suspended soil particles accounted for 85% of the runoff. Wauchope and Leonard (1980) classified several pesticides, including trifluralin, according to their availability index (i.e., the ratio of observed runoff to the amount applied) in treated fields. Trifluralin was placed in Class IV with an availability index of 300 m^2 ha kg^{-1}.

Gile et al. (1980) reported the absence of trifluralin in the groundwater of a laboratory model ecosystem 20 days after 0.28 kg/ha of the

compound was applied to foliage. Kearney et al. (1977) studied the fate of trifluralin in an aquatic micro-ecosystem. One hundred grams of soil containing 100 ppm trifluralin plus a radiolabeled tracer were placed in an aquarium and 4 ℓ of water, snails, algae and daphnids were added. The ^{14}C concentrations in water were monitored for 30 days. Fish were added on the 30th day and the radioactivity of all components was assayed on the 33rd day. The trifluralin concentrations (based on ^{14}C) in water, algae, snails (washed with distilled water), daphnids and fish were 0.0075, 2.07, 0.17, 0.66 and 0.24 ppm, respectively. No parent trifluralin was found in water or fish at the end of the experiment; the observed radioactivity was in the form of polar degradation products.

Schneider et al. (1977) reported on the fate of trifluralin injected into a static sandy aquifer. An aqueous solution of trifluralin (0.024 ppm) was pumped (81.3 m^3/hour) into a fine sand aquifer for 10 days. After a 10-day waiting period, water was pumped from the aquifer via observation wells drilled 9, 20 and 45 m from the injection site. Samples collected from the wells indicated a 98% recovery. No trifluralin was detected in the 45 m well. Trifluralin concentrations >0.024 ppm pumped from the injection well indicated that some adsorption to aquifer particles had occurred.

Walker (1981) studied the degradation of trifluralin (200 ppb) in samples of active and sterile bay water and sediment. All incubations were conducted in the dark at 25°C at pH 7.5±2. The average half-life of trifluralin in active and sterile bay water was 7.4 and 7.2 days, respectively. The average half-life of trifluralin in active and sterile sediment was 3.8 and 6.6 days, respectively.

Sunlight photodecomposition of trifluralin in aqueous solution has been reported by Crosby and Leitis (1973), Leitis (1973), Leitis and Crosby

/1974), and Zepp and Cline (1977). The rates of photolysis were greatest at pH 5.5-7.5 (Crosby and Leitis, 1973; Leitis, 1973). The photodecompcsition of trifluralin involves oxidative dealkylation, nitro group reduction and cyclization (Leitis and Crosby, 1974). The rate of photodecomposition of trifluralin was reduced 90-95% when it was adsorbed onto suspended soil particles (Leitis, 1973). Judging from the published BCF's (1060-6000), trifluralin is expected to bioaccumulate in fish (Verschueren, 1983). River fish exposed to trifluralin concentration on the order of 874 ng/ℓ experienced bioaccumulation (Spacie, 1975). Sanger, shorthead redhorse, golden redhorse, mussels and crayfish had whole body trifluralin concentrations of 10.3, 5.4, 3.2, 0.5 and 0.02 ppm, respectively. BCFs were estimated for sanger (5421), shorthead redhorse (2832), golden redhorse (1689) and fathead minnows (3261).

BCFs for trifluralin as high as 23,640 for algae and 17,872 in snails have been reported (Yockim et al., 1980; Metcalf and Sanborn, 1974).

3. EXPOSURE

Day et al. (1982) monitored agricultural workers engaged in trifluralin application. Personal breathing zone air samples were collected from applicators, formulation mixers, drivers and soil incorporators. Average trifluralin concentrations ranged from 0.12-62.7 µg/m³. Generally, the applicators, drivers and mixers had the highest exposures; the incorporators experienced the lowest exposures.

Water samples collected from the Wabash River 8 km downstream of the point where wastewater treatment effluent was discharged by an Eli Lilly trifluralin manufacturing facility contained 874 ng trifluralin/ℓ (Spacie, 1975).

Mittelman (1978) estimated the trifluralin exposure to workers involved in application/mixing/loading of the compound in a variety of agricultural crops. The inhalation and dermal ranges of exposure were 100-2754 µg/year and 7.0-196.6 µg/year, respectively. The U.S. EPA (1982) estimated the trifluralin vapor concentrations in air after application to field soil. The concentration at day 0 was 0.26 µg/m³ and declined to 0.01 µg/m³ 98 days after treatment.

Regelman (1981) estimated the trifluralin exposure to agricultural workers who re-enter a treated field. The ranges for inhalation and dermal exposures were 5.2-20.2 and 0.62-2.43 µg/year, respectively.

Regelman (1981) summarized data regarding reported residues of trifluralin on a variety of crops. Most commodities had residues below the limit of detection (<0.01 ppm). In carrots, peppermint oil and spearmint oil, the residues reported were 0.49-0.86, 0.57-1.71 and 0.57-1.71 ppm, respectively.

STORET contains trifluralin monitoring data from 511 selected stations. Trifluralin concentrations in water ranged from 0.1-51 µg/L. Trifluralin concentrations in sediment ranged from 4-5000 µg/kg with a mean value of 115 µg/kg. Trifluralin concentrations in fish ranged from 0.01-0.21 mg/kg with a mean value of 0.0196 mg/kg.

In 1977, the U.S. EPA was petitioned to suspend the registration of trifluralin because carcinogenic N-nitrosamines had been found to contaminate products containing trifluralin. After reviewing comments and the available data, the U.S. EPA issued a notice of intent to cancel all trifluralin registrations unless the total N-nitrosamine levels are <0.5 ppm (U.S. EPA, 1982).

4. PHARMACOKINETICS

4.1. ABSORPTION

Golab et al. (1969) administered trifluralin in the diet to ruminants (one lactating Holstein cow and one lactating goat). The cow received a diet containing 1 ppm trifluralin for 39 days, followed by a diet containing 1000 ppm trifluralin for an additional 13 days. The goat was fed a diet containing 1 ppm trifluralin for a total of 26 days. On day 12, [^{14}C]trifluralin, labeled in the trifluoromethyl group, was used. The compound was obviously absorbed following this route of exposure, since metabolites were found in the urine; however, the extent of absorption could not be calculated from the available data.

Emmerson and Anderson (1966) administered trifluralin (100 mg/kg in 0.5 ml corn oil) orally to male Harlan-Wistar rats. Experiments performed with bile duct-cannulated rats indicated that 40-50% of the administered compound was excreted in the feces without being absorbed.

No information was available on the absorption of trifluralin following inhalation or dermal exposure.

4.2. DISTRIBUTION

At the end of the feeding period, Golab et al. (1969) investigated the residues of trifluralin and trifluralin metabolites in a number of tissues of the cow. Fat tissue was found to contain 0.03 ppm trifluralin and 0.06 ppm alpha, alpha,alpha-trifluoro-N_4,N_4-dipropyl-5-nitro-toluene-3,4-diamine, a trifluralin metabolite. No residues were found in liver, kidney or heart tissue.

4.3. METABOLISM

Nelson et al. (1977) investigated the <u>in vitro</u> metabolism of [^{14}C]trifluralin by normal and phenobarbital-induced rat liver microsomes. They

4.3. METABOLISM

Nelson et al. (1977) investigated the *in vitro* metabolism of [^{14}C]trifluralin by normal and phenobarbital-induced rat liver microsomes. They identified a total of eight metabolites:

α,α,α-trifluoro-2,6-dinitro-N-propyl-p-toluidine;
α,α,α-trifluoro-2,6-dinitro-p-toluidine;
α,α,α-trifluoro-2,6-dinitro-N-(1-(3-hydroxy)-propyl)-p-toluidine;
α,α,α-trifluoro-2,6-dinitro-N-(1-(2-hydroxy)-propyl)-p-toluidine;
α,α,α-trifluoro-2,6-dinitro-N-propyl-N-(1-(3-hydroxy)-propyl)-p-toluidine;
α,α,α-trifluoro-2,6-dinitro-N-propyl-N-(1-(2-hydroxy)-propyl)-p-toluidine;
α,α,α-trifluoro-2,6-dinitro-N-ethyl-p-toluidine and
α,α,α-trifluoro-3,4-diamino-5-nitrotoluene.

Aliphatic hydroxylation, nitro reduction, N-dealkylation and cyclization to form a benzimidazole were the major metabolic routes involved.

Golab et al. (1969) measured the degradation of trifluralin by an artificial rumen fluid medium. The two major metabolites were identified as alpha-alpha,alpha-trifluoro-N_4,N_4-dipropyl-5-nitro-toluene-3,4-diamine and alpha-alpha,alpha-trifluoro-N_4,N_4-dipropyl-toluene-3,4,5-triamine. A number of more polar products were detected and the authors speculated that these were formed as a result of aromatic amine condensation. When the fecal excretion of metabolites in a cow fed a diet containing trifluralin was investigated (see Section 4.1.), these two major metabolites, alpha,-alpha,alpha-trifluoro-2,6-dinitro-N-propyl-p-toluidine and alpha,alpha,-alpha-trifluoro-2,6-dinitro-p-toluidine, were identified. The feces of goats dosed with trifluralin contained predominantly alpha,alpha,alpha-trifluoro-N_4,N_4-dipropyl-toluene-3,4,5-triamine; however, the urine also contained traces of alpha,alpha,alpha-trifluoro-2,6-dinitro-p-toluidine, alpha,alpha,alpha-trifluoro-N_4,N_4-dipropyl-5-nitrotoluene-3,4-diamine, alpha,alpha-trifluoro-5-nitro-N_4-propyl-toluene-3,4-diamine, alpha,alpha,-alpha-trifluorotoluene-3,4,5-triamine and possibly alpha,alpha,alpha-trifluoro-N_4-propyl-toluene-3,4,5-triamine.

Emmerson and Anderson (1966) investigated the metabolism of orally administered trifluralin (100 mg/kg bw) by male Harlan-Wistar rats. Only one metabolite, resulting from reduction of one of the nitro groups to an amine, was detected in the feces. Ten metabolites were isolated from the urine of these rats, of which three could be characterized. One of these metabolites was identified as the complete dealkylation product, alpha, alpha,alpha-trifluoro-2,6-dinitro-p-toluidine. The second was identified as alpha,alpha,alpha-trifluoro-5-nitro-N_4-propyl-toluene-3,4-diamine and the third as alpha,alpha, alpha-trifluoro-5-dinitrotoluene-3,4-diamine. The remaining metabolites could not be identified because of chemical instability. When trifluralin labeled with ^{14}C in the N-propyl group was administered, 19% of the dose was excreted as radiocarbon dioxide within 24 hours. The authors speculated that a large proportion of the metabolites observed in the feces were the result of microbial nitro-reduction in the gut.

4.4. EXCRETION

Golab et al. (1969) (see Section 4.1.) administered trifluralin labeled with ^{14}C in the trifluoromethyl group to a goat. Maximum levels were observed in the urine and feces on days 1 and 2 postexposure, respectively, and excretion was essentially complete within 6 days. The urine and feces accounted for 17.8 and 81.2% of the dose, respectively. No radioactivity was excreted in the milk and the high recovery values (99%) makes it unlikely that any significant amount was excreted as $^{14}CO_2$.

Emmerson and Anderson (1966) obtained essentially the same results in rats using $^{14}CF_3$-trifluralin. Excretion was essentially complete within 3 days, with 78% of the dose excreted in the feces and 22% in the urine. When the trifluralin labeled in the N-propyl group, excretion in expired

air, urine and feces accounted for 19.3, 25.7 and 43.2% of the dose, respectively, indicating the importance of N-dealkylation in the metabolism of trifluralin.

5. EFFECTS

5.1. CARCINOGENICITY

Any discussion of the carcinogenicity of trifluralin would be incomplete without a consideration of N-nitroso-di-n-propylamine (NDPA). NDPA exists as a probably unavoidable contaminant in all trifluralin-containing products. The currently used synthesis of trifluralin results in the production of <1 ppm NDPA (U.S. EPA, 1982). NDPA has been found to be carcinogenic in rats (Druckrey et al., 1967; Reznik et al., 1975), hamsters (Pour et al., 1973) and mice (Dickhaus et al., 1977), and concern for the health effects of NDPA is a major concern of the U.S. EPA in the consideration of registration of trifluralin (U.S. EPA, 1979).

Trifluralin has been tested for carcinogenicity by the National Cancer Institute (NCI, 1978). Technical grade trifluralin of >90% purity and containing 84-88 ppm NDPA was administered to groups of 50 male and 50 female Osborne-Mendel rats and B6C3F1 mice in their diet. The control groups for the mice contained only 20 animals of each sex, and for the rats, contained 50 animals of each sex. The rats received 13,000, 6500 or 0 ppm trifluralin for 22 weeks. After this time, the doses were lowered to 6500, 3250 and 0 ppm because of developing toxicity. Male mice received 4000, 2000 or 0 ppm throughout the study. Female mice received 9000, 4500 or 0 ppm for 18 weeks. After this time, the doses were reduced to 4500, 2250 or 0 ppm because of developing toxicity. Rats were maintained on the treatment diets for 78 weeks, followed by a 33-week observation period. The TWA dietary concentrations for the rats during the 78-week treatment period were 4125 ppm for the low-dose males and females, 8000 ppm for the high-dose males and 7917 ppm for the high-dose females. Mice were maintained on the treatment diets for 78 weeks followed by a 12-week observation period. The

TMA dietary concentrations for the mice during the 78-week treatment period were 2000 ppm for the low-dose males, 2740 ppm for the low-dose females, 3744 ppm for the high-dose males and 5192 ppm for the high-dose females.

Using the Fisher exact test, the combined incidence of follicular-cell adenomas and carcinomas of the thyroid was significantly elevated over controls in the low-dose female rats (P=0.028); however, no similar increase was observed in the high-dose group. There were no other statistically significant associations between trifluralin administration and tumor incidence in either sex of rats. The data are not sufficient to imply a carcinogenic potential of trifluralin in Osborne-Mendel rats.

In female mice, there was a dose-dependent, statistically significant increase in hepatocellular carcinomas in the treatment groups (Table 5-1). The incidence of alveolar/bronchiolar adenomas was also increased in these mice, but not in a dose-dependent manner. Squamous-cell carcinomas of the stomach were observed only in the treated groups; however, this incidence was not statistically significant. No statistically significant increase in specific tumor incidences were observed in male mice. Thus, it appears that technical-grade trifluralin induced hepatocellular carcinoma and possibly alveolar/bronchiolar adenomas and squamous-cell carcinomas of the stomach in female B6C3F1 mice. The possibility exists that the tumors observed in this study were due to NDPA rather than trifluralin.

Two other carcinogenicity studies, which are unpublished and classified as proprietary, are available to the U.S. EPA (U.S. EPA, 1979). Worth et al. (1966) fed diets containing 0, 20, 200, 2000 or 20,000 ppm trifluralin to groups of six male and six female Harlan-Wistar rats for 2 years. Survival was low in all groups. An FDA review (Schultz, 1967) concluded that the difference in ages at death was statistically significant. The

TABLE 5-1

Tumor Incidences in Female Mice in the
NCI Chronic Feeding Study of Trifluralin*

Tumor Type	Matched Control	Low-Dose	High Dose
Hepatocellular carcinoma	0/20 (p<0.001)	12/47 (p=0.009)	21/44 (p<0.001)
Hepatocellular adenoma	0/20	3/47	0/44
Hepatocellular carcinoma or adenoma	0/20 (p<0.001)	15/47 (p=0.002)	21/44 (p<0.001)
Alveolar/bronchiolar carcinoma	0/19	1/43	0/30
Alveolor/bronchiolar adenoma	0/19	6/43	3/30
Squamouscell carcinoma of stomach	0/20	4/45 (p=0.031)	1/44

*Source: Adapted from NCI, 1978

When <0.05, p values for the Fisher exact test are shown below incidence for treated groups, and p values for the Cochran-Armitage Test for linear trend are shown below the incidence for controls.

U.S. EPA's Carcinogen Assessment Group (CAG) concluded that the study did not provide evidence for carcinogenicity, but that the low number of animals initially involved and the high mortality precluded use of the study for safety evaluation. In a separate study, Worth et al. (1966) fed diets containing 0, 200, 1000 or 2000 ppm trifluralin to groups of 25 male and 25 female Cox rats for 2 years. There were no significant differences in number of survivors, food consumption, weight gain or blood chemistry between any of the groups. The only statistically significant pathological change was an increased rate of progressive glomerulonephrosis in all treated males. The CAG concluded that this study showed no evidence of carcinogenicity.

In September, 1980, Elanco submitted the results of a 2-year dietary carcinogenicity assay in B6C3F_1 mice and Fischer 344 rats to the EPA (U.S. EPA, 1982). This study used purified trifluralin containing <0.01 ppm NNPA. Groups of 80 male and 80 female mice were fed diets containing 563, 2250 or 4500 ppm. The controls consisted of 120 animals of each sex. The major effects observed were reduced bw and renal toxicity. They concluded, and the EPA agreed, that "there was no evidence that treatment induced increases of benign or malignant neoplasms" in the mice.

In the rat study, groups of 60 males and 60 females were fed diets containing 0, 813, 3250 or 6500 ppm purified trifluralin for 2 years. Elanco found significant dose-related increases in the incidence of malignant neoplasms in the kidneys of male rats at all doses (Table 5-2). There was also a dose-related increase in the incidence of benign bladder neoplasms in female rats, or in male and female rats combined, but not in male rats alone. There was also a high incidence of chronic renal disease and renal calculi. Elanco attributes the increase in urinary tract tumors to

TABLE 5-2

Tumor Incidence in Rats in the Elanco Chronic Feeding Study of Trifluralin[a,b]

Tumor Type and Site	Sex	Dose (in ppm) 0	813	3250	6500	Statistical Significance (Fisher Exact Test) (High Dose vs. Control)
Transitional cell papilloma and carcinoma (kidney and bladder)	male	0/60	3/60	3/60	6/60	0.014
	female	0/60	0/60	1/60	5/60	0.029
Follicular adenoma and carcinoma (thyroid gland)	male[d]	5/60	2/60	8/60	13/60	0.036[e]
Combined tumors[c] (kidney, bladder and/or thyroid)	male[c]	5/60	5/60	9/60	17/60	0.004

[a]Source: U.S. EPA, 1982

[b]Number of animals with tumors/number of animals in treatment or control group.

[c]Each rat had at least one tumor.

[d]Increase in tumor incidence is significant for males only.

[e]Dose response is significant at a level $p<0.01$ when computed by the Cochran-Armitage Test.

the presence of renal calculi rather than considering the tumors to be a result of trifluralin treatment; however, the EPA differs with this assessment. The EPA review of this study found significant increases in tumors of the urinary transitional epithelium in both male and female rats and in follicular tumors of the thyroid in male rats.

5.2. MUTAGENICITY

Data on the in vitro mutagenicity of trifluralin are summarized in Table 5-3. In vitro testing of the mutagenicity of trifluralin have produced uniformly negative results in a wide variety of tests, both with and without activation by mammalian activating systems.

Trifluralin has, however, been demonstrated to increase the incidence of nondisjunction in vivo. Murnik (1978) and Bryant and Murnik (1979) scored the progency of both larval-fed and adult-fed male Drosophila melanogaster (0.01% trifluralin in modified Carpenter's medium) for breakage, loss or nondisjunction of the X and Y chromosomes and mosaicism. The rate of XXY nondisjunction was significantly increased in the larval-fed group and the number of mosaics was increased relative to controls. Trifluralin has also been reported to increase nondisjunction and to produce deletion of the paternal X,Y chromosome in the progeny of larval-fed males (Foureman, 1981).

Sentein (1977) investigated the mechanism by which trifluralin induces nondisjunction. He found that trifluralin inhibits cytokinesis by interfering with the action of the asters. The biochemical changes responsible for this inhibition were not elucidated.

Nehez et al. (1980, 1981) administered Olitref, containing 26% trifluralin, to male CFLP mice at doses of 1/100, 1/3 and 2/3 of the LD_{50} (dose and route not otherwise specified in these abstracts). Under these conditions, they obtained an increase in chromosomal abnormalities of bone

TABLE 5-3

In Vitro Mutagenicity of Trifluralin

Assay	Indicator Organism	Application	Concentration	Activation	Response	Reference
Reverse mutation	*S. typhimurium* NR	spot test	NA	-	-	Anderson et al, 1972
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA100	spot test	NA	+/-	-	Eisenbeis et al., 1981
Reverse mutation	*S. typhimurium* TA1535, TA1536, TA1537, TA1538	plate incorporation	NR	-	-	Shirasu et al., 1976
Reverse mutation	*S. typhimurium* TA100, TA98, TA1535, TA1537, TA1538	plate incorporation	NR	+/-	-	Moriya et al., 1983
Reverse mutation	*S. typhimurium* NR	NR	NR	+/-	-	Simmon et al., 1976
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	up to 10 mg/plate	+/-	-	Waters et al., 1982
Reverse mutation	*E. coli* WP2	spot test	NR	-	-	Shirasu et al., 1976
Reverse mutation	*E. coli* WP2	plate incorporation	NR	+/-	-	Moriya et al., 1983
Reverse mutation	*E. coli* WP2	plate incorporation	up to 10 mg/plate	-	-	Waters et al., 1982

TABLE 5-3 (cont.)

Assay	Indicator Organism	Application	Concentration	Activation	Response	Reference
Differential toxicity	*E. coli* NR	NR	NR	+	-	Simmon et al., 1976
Differential toxicity	*E. coli* p3478, W3110	spot Test	NR	-	-	Waters et al., 1982
Rec-Assay	*B. subtilis* H17rec$^+$, M45rec$^-$	spot test	NR	-	-	Shirasu et al., 1976
Rec-assay	*B. subtilis* H17rec$^+$, M45rec$^-$	spot test	NR	-	-	Waters et al., 1982
Rec-assay	*B. subtilis* NR	NR	NR	-	-	Simmon et al., 1976
Mitotic recombination	*S. cerevisiae* NR	NR	NR	+	-	Simmon et al., 1976
Mitotic recombination	*S. cerevisiae* D3	NR	NR	+/-	-	Waters et al., 1982
Unscheduled DNA synthesis	human lung fibroblast	liquid suspension	NR	+/-	-	Waters et al., 1982

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marrow cells, evidence for gametic mutation in the spermatocyte test, positive results in the dominant lethal assay and alterations of F_1 embryonic chromosomes.

N-nitroso-di-n-propylamine, a common contaminant of trifluralin, has been demonstrated to be mutagenic in a number of bacterial and cell culture systems (Kuroki et al., 1977; Yahagi et al., 1977; Nakajima et al., 1974; Andrews et al., 1978; Olajos and Cornish, 1976). Though this compound can induce point mutations, there is no indication that it may be responsible for the nondisjunction observed with trifluralin.

5.3. TERATOGENICITY

Beck (1977, 1981) treated five pregnant CD-1 mice on days 6-15 of gestation with 1 mg trifluralin/kg/day by gavage. The pups were sacrificed at 62±2 days postpartum and examined for skeletal abnormalities. A significant increase in the number of skeletal abnormalities was observed following trifluralin treatment as compared with untreated controls, including the occurrence of 14 ribs, accessory foramina in the cervical vertebrae, undoubled foramen ovale and parted frontals. No gross abnormalities were noted at birth.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects were not located in the available literature.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In the NCI carcinogenicity bioassay (see Section 5.2.), Osborne-Mendel rats and B6C3F1 mice were fed diets containing 4125-8000 ppm and 2000-5192 ppm trifluralin, respectively. During the 2 years of the study, no specific non-carcinogenic pathological changes other than decreased weight gain were noted in either rats or mice. An increased mortality was noted in the high-

dose female mice; however, this may have been due to the increase in hepatocellular carcinomas in this group.

5.6. OTHER RELEVANT INFORMATION

The reported acute LD_{50} values are summarized in Table 5-4. Trifluralin exhibits low toxicity in all species tested; however, Done (1979) states that human exposure results in moderate, ill-defined toxicity.

Hertel et al. (1981) found that trifluralin inhibits calcium accumulation by rat liver mitochondria. The observed decrease in accumulation resulted from an increase in the rate of ruthenium red-insensitive Ca^{2+} efflux.

TABLE 5-4

Acute LD_{50} Values for Trifluralin

Species	Route	LD_{50} (mg/kg)	Reference
Rat	oral	>10,000	Martin and Worthing, 1977
Mouse	oral	5,000	NIOSH, 1983
Dog	oral	>2,000	Martin and Worthing, 1977
Rabbit	oral	>2,000	Martin and Worthing, 1977
Microtus canicaudus	oral	>5,000	Cholakis et al., 1981
Microtus orchrogaster	oral	>5,000	Cholakis et al., 1981

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity of trifluralin has been determined for many species of freshwater fish by various investigators (Table 6-1). The 96-hour LC_{50} values range from 0.0084 mg trifluralin/ℓ, determined at 29°C in the bluegill sunfish (Cope, 1965a), to 2.20 mg/ℓ at 22°C in the channel catfish (Johnson and Finley, 1980). Temperature is an important influencing factor on the aquatic toxicity of trifluralin. As temperature and duration of exposure increase, the lethal effects of trifluralin increase (Pimentel, 1971). This factor is quite evident from data reported by Cope (1965a) in which the 24- and 96-hour LC_{50} values for bluegills exposed at 7°C were 1.30 and 0.028 mg/ℓ, respectively (Table 6-1). At 29°C, bluegills were much more sensitive to trifluralin, with 24- and 96-hour LC_{50} values of 0.01 and 0.0084 mg/ℓ, respectively (Cope, 1965a). During toxicity testing of trifluralin, Johnson and Finley (1980) reported that temperature, pH and water conditions did not greatly effect lethality to fish. The most influential factor was the age of fish. In rainbow trout swim-up fry and fingerlings, trifluralin was up to 20 times more toxic than in yolk-sac fry (Johnson and Finley, 1980).

The acute lethal effects of trifluralin have been determined in several species of freshwater and marine crustaceans and stonefly naiads (Table 6-2). The 48-hour LC_{50} values for daphnids range from 0.193 mg trifluralin/ℓ for Daphnia magna (Macek et al., 1976) to 0.900 mg/ℓ for Simocephalus serrulatus (Johnson and Finley, 1980). Other crustaceans, such as the glass shrimp, scud and sowbug, had 48-hour LC_{50} values between 1.20-5.60 mg/ℓ (Table 6-2). The crayfish, Orconectes nais, was the most resistant species, with a 48-hour LC_{50} of 50.00 mg/ℓ (Sanders, 1970).

TABLE 6-1

Acute Lethal Effects of Trifluralin to Freshwater Fish

Species	Duration (hour)	Concentration (mg/L)	Method	Effect	Reference
Bluegill sunfish, Lepomis macrochirus	24	0.100	static	LD_{50}	Cope, 1965b
	48	0.96	static	LC_{50}	
	96	0.68	static	LC_{50}	
Bluegill sunfish, L. macrochirus	NR	0.0582	static	LC_{50}	Parka and Worth, 1965
Bluegill sunfish, L. macrochirus	24	1.30	static, 7°C	LC_{50}	Cope, 1965b
	24	0.01	static, 29°C	LC_{50}	
	96	0.0280	static, 7°C	LC_{50}	
	96	0.0084	static, 29°C		
Bluegill sunfish, L. macrochirus	48	0.019	static	LC_{50}	Cope, 1966
Bluegill sunfish, L. macrochirus	96	0.058	static, 22°C	LC_{50}	Johnson and Finley, 1980
Bluegill sunfish, L. macrochirus	24	0.130	static, 23.8°C	LC_{50}	Macek et al., 1969
	96	0.047	static, 23.8°C	LC_{50}	
Rainbow trout, Salmo gairdneri	24	0.21	static	LC_{50}	Cope, 1965a
	48	0.13	static	LC_{50}	
	96	0.86	static	LC_{50}	
Rainbow trout, S. gairdneri	48	0.011	static	LC_{50}	Cope, 1966
Rainbow trout, S. gairdneri	96	0.041	static, 12°C	LC_{50}	Johnson and Finley, 1980
Rainbow trout, S. gairdneri	24	0.098	static, 12.7°C	LC_{50}	Macek et al., 1969
	96	0.042	static, 12.7°C	LC_{50}	

TABLE 6-1 (cont.)

Species	Duration (hour)	Concentration (mg/L)	Method	Effect	Reference
Fathead minnow, Pimephales promelas	NR	0.0934	static	LC_{50}	Parka and Worth, 1965
Fathead minnow, P. promelas	96	0.105	static, 18°C	LC_{50}	Johnson and Finley, 1980
Fathead minnow, P. promelas	288	0.115	flow-through	LC_{50}	Macek et al., 1976
Goldfish, Carassius auratus	NR	0.585	static	LC_{50}	Parka and Worth, 1965
Goldfish, C. auratus	96	0.145	static, 18°C	LC_{50}	Johnson and Finley, 1980
Goldfish, C. auratus	48	0.85	NR	LC_{50}	Hashimoto and Nishiuchi, 1981
Charnel catfish, Ictalurus punctatus	96	2.20	static, 22°C	LC_{50}	Johnson and Finley, 1980
Channel catfish, I. punctatus	96	0.417	static	LC_{50}	McCorkle et al., 1977
Largemouth bass, Micropterus salmoides	96	0.075	static, 18°C	LC_{50}	Johnson and Finley, 1980
Carp, Cyprinus carpio	48	1.00	NR	LC_{50}	Hashimoto and Nishiuchi, 1981
Medaka, Oryzias latipes	48	0.43	NR	LC_{50}	Hashimoto and Nishiuchi, 1981
Pond loach, Misgurnus anguillicandatus	48	0.35	NR	LC_{50}	Hashimoto and Nishiuchi, 1981
Harlequin fish, Rasbora heteromorpha	24	1.00	static	LC_{50}	Alabaster, 1969
	48	0.60	static	LC_{50}	

NR = Not reported

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TABLE 6-2

Acute Lethal Effects of Trifluralin to Other Aquatic Species

Species	Duration (hour)	Concentration (mg/l)	Method	Effect	Reference
Water flea, Daphnia magna	48	0.193	static	LC_{50}	Macek et al., 1976
Water flea, D. magna	48	0.56	static	LC_{50}	Sanders, 1970
Water flea, D. magna	48	0.560	static	EC_{50}, immobilization	Johnson and Finley, 1980
Water flea, D. pulex	48	0.240	static	EC_{50}, immobilization	Sanders and Cope, 1966
Water flea, D. pulex	48	0.625	static	EC_{50}, immobilization	Johnson and Finley, 1980
Scud, Gammarus fasciatus	48	1.80	static	LC_{50}	Sanders, 1970
Scud, Gammarus lacustris	24 48 96	8.80 5.60 2.20	static static static	LC_{50} LC_{50} LC_{50}	Sanders, 1969
Scud, G. fasciatus	96	2.200	static	LC_{50}	Johnson and Finley, 1980
Simocephalus serrulatus	48	0.450	static	EC_{50}, immobilization	Sanders and Cope, 1966
Simocephalus serrulatus	48	0.900	static	EC_{50}, immobilization	Johnson and Finley, 1980

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TABLE 6-2 (cont.)

Species	Duration (hour)	Concentration (mg/l)	Method	Effect	Reference
Soubug, Asellus brevicaudus	48	2.00	static	LC_{50}	Sanders, 1970
Seed shrimp, Cypridopsis vidua	48	0.25	static	LC_{50}	Sanders, 1970
Glass shrimp, Palaemonetes kadiakensis	48	1.20	static	LC_{50}	Sanders, 1970
Crayfish, Orconectes nais	48	50.00	static	LC_{50}	Sanders, 1970
Stonefly naiad, Pteronarcys californica	24	13.00	static	LC_{50}	Sanders and Cope, 1968
	48	4.20	static	LC_{50}	
	96	3.00	static	LC_{50}	
Stonefly naiad, P. californica	96	2.800	static	LC_{50}	Johnson and Finley, 1980
Oligochaete worm, Lumbricalus variegatus	48	>0.3	static	LC_{50}	Bailey and Liu, 1980
	96	>0.3	static	LC_{50}	Bailey and Liu, 1980
Crayfish, Procambarus clarkii	96	12.0	static	LC_{50}	Naqui and Leung, 1983

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The 48- and 96-hour LC_{50} values for trifluralin in a benthic oligochaete worm, Lumbriculus variegatus, were both >0.3 mg/ℓ (Bailey and Liu, 1980).

6.2. CHRONIC EFFECTS

The effects of trifluralin exposure on developmental stages of the sheepshead minnow, Cyprinodon variegatus, were determined by Couch et al. (1979). Zygote, embryo, larvae, juvenile and adult stage C. variegatus were exposed to trifluralin at 0.0012-0.031 mg/ℓ. Minnows exposed at ≥0.0055 mg/ℓ trifluralin concentrations from the zygotic stage through 28 days of exposure developed vertebral dysplasia.

Fathead minnows, Pimephales promelas, were exposed to trifluralin at 0.0015, 0.0019, 0.0051, 0.0082 and 0.0165 mg/ℓ for up to 61 weeks (Macek et al., 1976). All fish exposed at 0.0165 mg/ℓ had died by 60 days of exposure. All fish exposed at 0.0085 mg/ℓ had died by 158 days. Mortality in those exposed at 0.0051 mg/ℓ was greater than in controls by 61 weeks. Spawning activity was delayed and occurred only sporadically in the surviving fish exposed to 0.0051 mg trifluralin/ℓ (Macek et al., 1976). No effect on mortality, spawning or reproductive success was noted in groups exposed to 0.0019 or 0.0015 mg trifluralin/ℓ. Based on these chronic studies, the authors (Macek et al., 1976) suggested that the maximal acceptable toxicant concentration for trifluralin in this species was near 0.0019 mg/ℓ.

The effects of trifluralin, administered as an emulsifiable concentrate in acetone at 0.5, 0.25 and 0.01 mg/ℓ, were determined in salmon parr, Salmo salar, exposed for 11 hours and followed for 12 months (Wells and Cowan, 1982). This laboratory study was conducted to model an accidental spill in which brown trout, Salmo trutta, developed spinal dysplasia several

months after an acute trifluralin exposure. Fish exposed at 0.5 and 0.25 mg trifluralin/ℓ lost equilibrium during exposure but recovered after several hours. Within 10 days, vertebral damage was evident in parr treated at 0.5 and 0.25 mg/ℓ. Skeletal deformities that developed included compressed vertebrae, which caused parr to actually decrease in length, vertebral fusion and hypertrophic vertebral development. Vertebrae were the only bones affected by the trifluralin exposure.

Continuous exposure to trifluralin at 0.0072, 0.0140, 0.0276 and 0.0527 mg/ℓ for 64 days significantly reduced survival of Daphnia magna during the 3-generation study (Macek et al., 1976). Survival was cumulatively reduced in the three generations with no survivors at the highest two dose groups after a total exposure of 64 days. At 0.0140 and 0.0072 mg trifluralin/ℓ, survival in the third generation after 64 days total exposure was 15 and 0%, respectively, while 75% survival was noted in controls. Survival in a group exposed at 0.0024 mg trifluralin/ℓ was not different from controls throughout the 64-day study (Macek et al., 1976). The production of young was reduced in all three generations of Daphnia exposed at $\geq$0.0072 mg trifluralin/ℓ. Based on these chronic studies, the maximal acceptable toxicant concentration for trifluralin to Daphnia magna was near 0.0024 mg/ℓ (Macek et al., 1976).

Zoea, juveniles and adults of the Dungeness crab, Cancer magister, were exposed to trifluralin at 0.0026-0.590 mg/ℓ to determine the most sensitive developmental stage and the maximal acceptable toxicant concentration for that stage (Caldwell et al., 1979). Larval stages were the most sensitive, having at least 50% mortality within 5 days at 0.220 mg trifluralin/ℓ. Zoeal development was slightly delayed at 0.22 mg/ℓ. At 0.026 mg trifluralin/ℓ, no toxic effects were noted. Juvenile crabs

survived for up to 80 days at 0.590 mg/ℓ and adults exposed at 0.30 mg trifluralin/ℓ survived for 85 days. Egg hatching and prezoeal stages were not affected at 0.33 mg/ℓ. The authors suggested that the maximal acceptable toxicant concentration for trifluralin in C. magister was between 0.026 and 0.220 mg/ℓ. In another report, Caldwell (1979) suggested a maximal acceptable toxicant concentration of 0.015 mg trifluralin/ℓ in C. magister.

6.3. PLANT EFFECTS

Growth of algae, Oedogonium cardiacum, was greatly inhibited by trifluralin at 0.0216 mg/ℓ (Yockim et al., 1980). After 30 days, the mat was ~2 cm in exposed algae, while 30 cm algal mats had grown in controls. A dose-dependent reduction in cell numbers and cellular damage was reported in trifluralin-exposed algae (Czeczuga et al., 1977).

6.4. RESIDUES

The BCF for trifluralin in fathead minnow, Pimephales promelas, exposed for 61 weeks at 0.0051, 0.0019 and 0.0015 mg/ℓ were 961, 1333 and 889, respectively (Macek et al., 1976). Kanazawa (1982) reported a BCF of 3142, determined in topmouth gridgeon, Pseudorasbora parva, for trifluralin. Isensee and Yockim (1980) and Yockim et al. (1980) reported on the influence of toxicant concentration, duration of exposure and experimental conditions (static or flowing) on the bioconcentration of trifluralin. In the mosquito fish, BCFs ranged from 68-8750 and were generally greater in flowing-systems within a few days when exposure levels were low (0.001 mg/ℓ). The range for BCFs in Daphnia magna, algae, Oedogonium cardiacum and snails, Helosoma sp., were 0-1293, 138-34,811 and 0-2718, respectively (Isensee and Yockim, 1980; Yockim et al., 1980).

Spacie and Hamelink (1979) reported on the occurrence and accumulation of trifluralin in Wabash River, Lafayette, Indiana, and several species of

fish therein. Trifluralin levels gradually decreased with distance from a chemical manufacturing plant discharge. The lowest levels reported, 0.00026 µg/l, were collected 64 km downstream from the plant. Levels within 1 km of the plant discharge were as high as 548 µg/l 1 week after an accident within the plant, but under normal conditions were 0.210-8.04 µg/l (Spacie and Hamelink, 1979). Levels of trifluralin in golden redhorse, Moxostoma erythrurum, were as high as 440.1 mg/kg of fat. Six other species of fish (sanger, Stizostedion canadense; river carpsucker, Carpoides carpio; quillback, Carpoides cyprinus; freshwater drum, Aplodinotus grunniens; carp, Cyrpinus carpio; and channel catfish, Ictalurus punctatus) had levels >100 mg trifluralin/kg fat. Fish captured upstream from the discharge site had relatively low levels of trifluralin (Spacie and Hamelink, 1979).

Brown trout, Salmo trutta, killed by a trifluralin spill in Scotland contained 11.8 mg trifluralin/kg muscle tissue (Wells and Cowan, 1982). Laboratory studies modeling this type of accident were used to determine a half-life of trifluralin in salmon parr, Salmo salar, of 40.5 days (Wells and Cowan, 1982).

6.5. OTHER RELEVANT INFORMATION

Pertinent data regarding the toxic effects of trifluralin on aquatic organisms were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

No TLV values have been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 1980). With few exceptions, the U.S. EPA has established tolerances for residues in or on raw agricultural commodities of 0.05 ppm (40 CFR 180.207). The exceptions are carrots (1.0 ppm), alfalfa hay (0.2 ppm), Mung bean sprouts (2.0 ppm) and peanut hulls (0.1 ppm).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of trifluralin were not located in the available literature.

8. RISK ASSESSMENT

Two studies are available from which an estimate of carcinogenic risk could be derived (NCI, 1978; U.S. EPA, 1982). The U.S. EPA's Carcinogen Assessment Group (CAG) has analyzed the results of an unpublished Elanco study in which purified trifluralin, containing <0.01 ppm NDPA, was tested. The CAG fitted the results of this study to the linearized multistage model and derived a human q_1^* (carcinogenic potency factor) of 7.7×10^{-3} $(mg/kg/day)^{-1}$, based on the combined incidence of kidney, urinary bladder and thyroid tumors in male Fischer 344 rats receiving diets containing 0, 813, 3250 or 6500 ppm purified trifluralin for 2 years (see Section 5.1.). The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 1.3×10^{-3} mg/kg/day, or 0.1×10^{-2} mg/day for a 70 kg human.

Since commercially available trifluralin is contaminated with dipropylnitrosamine (NDPA), which is ~3 times as carcinogenic as trifluralin (U.S. EPA, 1982), the carcinogenicity studies using a trifluralin/NDPA mixture may also be relevant to risk assessment. The National Cancer Institute's bioassay (NCI, 1978) can be used to estimate the carcinogenicity of trifluralin contaminated with NDPA. The trifluralin used in this study contained at least 84 ppm NDPA, which is much greater than the levels produced using current synthesis methods (<1 ppm). Since proposed EPA registration requirements demand that NDPA contamination be <1 ppm in the commercial product and that total N-nitrosamine concentrations be <0.5 ppm in formulations (U.S. EPA, 1982), this study should produce a conservative estimate of the risk resulting from exposure to commercial trifluralin mixtures. The data for the induction of hepatocellular carcinoma in female mice (NCI, 1978) were used to estimate a q_1^* (see Appendix B). Assuming that a mouse

consumes the equivalent of 13% of its body weight per day as food, the doses for this study were 356 and 675 mg/kg/day for the low and high dose groups, respectively. Applying a correction factor (1e/Le) to correct for the difference between the length of exposure (1e) and the length of the experiment (Le), the average daily doses were 309 and 585 mg/kg/day for the low and high dose groups, respectively. Based on the production of hepatomas in female B6C3F1 mice, a carcinogenic potency factor (q_1^*) of 2.9×10^{-2} $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 3.4×10^{-4} mg/kg/day or 2.4×10^{-2} mg/day for a 70 kg human.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data, but no change in the above risk assessment was necessitated.

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APPENDIX A:
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in July, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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APPENDIX B:

Cancer Data Sheet for Derivation of q_1^*

Compound:	Trifluralin
Reference:	NCI, 1978
Species, Strain, Sex:	mouse, B6C3F1, female
Body Weight:	0.027 (average measured)
Length of Exposure (l_e)	= 546 days
Length of Experiment (L_e)	= 630 days
Lifespan of Animal (L)	= 730 days
Tumor Site and Type:	liver, hepatocellular carcinoma
Route, Vehicle:	oral, feed

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence No. Responding/ No. Tested (or Examined)
0	0	0/20
2740 ppm	309	12/47
5192 ppm	585	21/44

Human $q_1^* = 2.92 \times 10^{-2}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 3.42×10^{-4} mg/kg/day = 2.39×10^{-2} mg/day for 70 kg man